REMARKS

This Reply is responsive to the Office Action dated April 10, 2002. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

I. Status of the Claims

Claims 55-112 were pending in this application at the time of the Office Action dated April 10, 2002. In this regard, the Office Action indicates on the front page that claims 55-111 are pending. However, claim 112 was added by way of a Supplemental Amendment filed on July 30, 2001. Applicants respectfully request that the Examiner check the file for the presence of this amendment, and let Applicants know whether a copy needs to be submitted. It appears that claim 112 should be grouped with the elected invention.

Claims 60, 61, 65, 66, 69-71, 73-75, 77-79, 81, 82, 84, 85, 88, 91-97, 107, 108, 110 and 111 were withdrawn from consideration as being directed to a non-elected invention. In addition, Applicants elected subject matter including attachment molecules comprising proteins and glycoproteins, endothelial cells, mannose, selectin or integrin, ICAM-1 and Candida in the Response to Restriction Requirement filed May 17, 2001. For the Examiner's convenience, attached to this Reply is a summary of the claims currently under examination that shows the elected subject matter in bold, and that also depicts the amendments entered above.

As a result of this amendment, new claims 113 and 114 have been entered and no claims have been canceled. These claims correspond to the elected invention, as

discussed in more detail below. Accordingly, claims 55-114 are now pending, of which claims 55-59, 62-64, 67, 68, 72, 76, 80, 83, 86, 87, 89, 90, 98-106, 109 and 112-114 are currently under examination.

II. Amendments to the Specification and the Claims

The specification was amended above to include a new title and a summary of related applications as requested in the Office Action. In addition, the sepcification was amended to correct various typographical errors, and to include reference to trademarks as requested in the Office Action. Applicants believe that no prohibited new matter was added by way of these amendments.

Claims 58 and 105 were amended to clarify that the claimed pathogen adhesin molecule "functionally" mimics "a ligand for said host adhesion molecule." Support for the phrase "functionally mimics" may be found at page 14, line 30. Support for the phrase "a ligand for said host adhesion molecule" may be found, for instance, in Figure 1, and on page 17, lines 13-15 of the specification. The term "ligand" is used in the phrase to distinguish over the "host adhesion molecule" already recited in claim 55. However, it should be understood that the ligand for the host adhesion molecule recited in claim 55 would also be considered to be a host adhesion molecule.

Claims 62, 64 and 109 were amended to clarify the claim language in view of the elected subject matter. For instance, Applicants have elected in part to prosecute claims wherein the host adhesion molecule is a receptor for a host ligand that is a selectin or an integrin (see claims 59 and 106). When the host ligand is an integrin, the host adhesion molecule may be a member of the immunoglobulin superfamily, for instance ICAM-1, as

recited and elected in claims 62 and 109. Support for this amendment, which clarifies an aspect of the elected invention, may be found, for instance, at page 31, lines 24-27.

Similarly, when the host ligand is a selectin as recited in claim 59, the host adhesion molecule may be a carbohydrate, for instance mannose, as recited and elected in claim 64. Claim 64 was amended to clarify this relationship, with support being found at page 15, lines 9-11. Claim 64 was also amended to depend on claim 59 to provide appropriate antecedent basis, and was also amended include the phrase "presents a residue" to maintain consistency with claim 99.

Finally, new claims 113 and 114 were added which specify that the pathogen adhesin molecule binds to a host adhesion molecule that binds to a selectin or integrin, respectively. Support for new claims 113 and 114 may be found in original claims 6 and 10, respectively. Claims 113 and 114 are directed to the elected subject matter, since Applicants have elected to prosecute claims where the host adhesion molecule is a receptor for a host ligand that is a selectin or an integrin (see claims 59 and 106). Since pathogen adhesin molecules falling within the scope of the elected claims would therefore include PAMs that bind to host adhesion molecules that also bind to selectins or integrins, the new claims are directed to elected subject matter.

No prohibited new matter has been added by way of any of these amendments.

III. Office Action

A. Drawings

On page 3, in paragraph number 3, the Office Action makes reference to the attached form PTO-948 and indicates that the drawings fail to comply with 37 CFR 1.84.

Applicants have made the requisite corrections to the drawings and are filing concurrently with this Reply a separate transmittal letter addressed to the Official Draftsperson with the corrected drawings attached.

B. Specification

On page 4, in paragraph number 4, the Office Action suggests that Applicants should amend the first line of the specification to update the status of the priority documents. This amendment has been entered above.

In paragraph 5, the Office Action suggests that a new title is warranted. Applicants have replaced the title by way of amendment above.

In paragraph 6, the Office Action states that the application does not include an Abstract of the Disclosure. However, Applicants' copy of the application shows that there is an Abstract on page 93. If the Office copy of the application does not include page 93, Applicants respectfully request that the Examiner alert Applicants as to the missing page and Applicants will supply the requisite Abstract.

In paragraph 7, the Office Action states that the application should be reviewed and all spelling errors and trademark designations should be corrected. Applicants have reviewed the specification as requested and have amended all inadvertent errors and trademark designations that were found.

C. Claims - Rejection Under 35 U.S.C. §102(e)

Claims 55-59, 62-64, 67, 68, 72, 76, 80, 83, 86, 87, 89, 90, 98-106 and 109 were rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Cutler et al. (U.S.

Patent No. 5,578,309). According to the Office Action, Cutler et al. teach Candida albicans vaccines that anticipate the claimed and elected invention. In particular, the Office Action states that the claimed functional limitations encompassing the elected invention comprising proteins, glycoproteins, endothelial cells, mannose, selectin or integrin, ICAM-1 and Candida (as well as specificity such as the claimed shear conditions) would be inherent properties of the referenced Candida vaccines.

Applicants respectfully note that the specification of the present application has been amended above to indicate that the present application is a continuation-in-part of the application that issued as U.S. Patent 5,578,309. Accordingly, the '309 patent cannot be cited as art against the present application. In view of this priority claim, withdrawal of the rejection under 35 U.S.C. §102(e) based on Cutler et al. is respectfully requested.

This reply is fully responsive to the Office Action dated April 10, 2002. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, he is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,

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Date: August 12, 2002

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APPENDIX

The following amendments were entered above:

IN THE SPECIFICATION

The paragraph at page 3, line 2, was amended as follows:

An object of the present invention is to provide a vaccine comprising a microbe targeting and attachment molecule which mimics a [target] host cell molecular address such as adhesion proteins, lipid molecules or carbohydrate molecules.

The paragraph at page 3, line 28, was amended as follows:

Advantageously, the invention provides a therapeutic peptide comprising a molecule which mimics the adhesion molecule of a pathogen and interacts with receptor molecules of a cell selected from the group consisting of leukocytes, endothelial cells, epithelial cells and other target cells of the host. The therapeutic peptide molecule may react specifically with receptor (ligands) of host adhesion [molecule] molecules. Conversely, the invention provides a therapeutic peptide or carbohydrate comprising a molecule which mimics the adhesion molecule of a host cell and interacts with (blocks) the adhesion molecules of a pathogen.

The paragraph at page 5, line 20, was amended as follows:

The attachment molecule may resemble a selectin, such as a molecule substantially and [functially] functionally similar to a selectin. In a preferred embodiment the selectin molecule is selected from those similar to E, L and P selectins.

The paragraph at page 8, line 19, was amended as follows:

The assay for detection, identification and enumeration of respiring microorganisms comprises the steps of:

a) passing a microbial sample through a collecting device to capture the cells;

b) adding to the collecting device a fluorochrome dye specific for the detection of respiring cells and allowing the dye to incubate;

c) treating the collected sample with a reactive fluorescent antibody which reacts with a microorganism of interest present in the microbial sample;

d) mounting said collecting device for examination by fluorescence microscopy in which a suitable light system is used to excite the fluorochrome dye and fluorescent antibody to fluoresce; and

e) quantifying [,] the fluorescence as a [masure] <u>measure</u> of the amount of said respiring target microbial cells.

Preferably the fluorochrome dye specific for the detection of respiring microbe is taken up by respiring microorganisms and reduced to insoluble formazan crystals by the cytochrome system of said microbes. More preferably the fluorochrome dye specific for the detection of respiring cells is a tetrazolium compound. Most preferred is tetrazolium compound which is 5-cyano-2,3-ditolyl tetrazolium chloride (CTC).

The paragraph at page 10, line 26, was amended as follows:

The peptide alternatively reacts with <u>a</u> receptor of the cytogene or chemokine family of host adhesion molecules or mimics the host adhesion molecule and interacts with adhesion molecules of the pathogen.

The paragraph at page 10, line 30, was amended as follows:

The inventors have found that naturally occurring endogenous peptide antibiotics of vertebrates act as an effective deterrent to viral, bacterial, fungal, and parasitic infections. Gene-encoded peptide antibiotics are ubiquitous components of host defenses in mammals, birds, amphibian, insects, and plants. Their *de novo* synthesis of release from storage sites can be induced rapidly, which makes them particularly important in the initial phases of resistance to microbial invasion. The endogenous anti-microbial peptides of animals are usually products of single genes and are synthesized as [preproproteins] <u>preproteins</u>. Multistep processing yields the mature peptide or group of peptides, which can act by inducing microbial membrane permeabilization or by adhesion to the microbial surface. The adhesive peptides act as lectins binding to the carbohydrates or lipids presented on the surface of infectious microbes thus making the organism more susceptible to immune detection and clearance. These binding peptides may also act to block the microbial host adhesion events leading to infection.

The paragraph at page 12, line 8, was amended as follows:

Naturally occurring, or engineered, mAbs or peptides with [anti-adhesives] <u>anti-adhesive</u> properties targeting host-parasite adhesion associated signaling with adhesion are effective for producing diagnostics, therapeutics and vaccines for host infections requiring microbial binding to host tissues.

The paragraph at page 12, line 15, was amended as follows:

Many pathogens trafficking through the vascular system use adhesion pathways operating under shear as a means of seeding various tissues. The inventors believe this concept is universally applicable and show the use of host adhesion pathways unique to different anatomical systems (respiratory, gastrointestinal tract, urinary tract, etc.) by a given pathogen. Thus, a new approach to [the] defining the virulence of many bacterial, viral, fungal and parasitic organisms may be directed to the detection and characterization of various prokaryotic and eukaryotic adhesion proteins that infiltrate the host's communications network. Several studies on different host-parasite relationships reveal how pathogens use the cell-cell adhesion systems of the host during the course of an infection. The results of some salient studies are presented to illustrate the types of functional mimicry that has evolved to allow a microbe to infiltrate the host cell-cell networks and to direct the course of infection.

The paragraph at page 13, line 9, was amended as follows:

Although it is clear that protein-carbohydrate interactions control a myriad of biological events, the low binding constants for protein-carbohydrate couples [has] <u>have</u> raised questions regarding the precise role of carbohydrate ligands in biological communication. However, a model for microbial toxin-host cell interaction proposed by St. Hilaire *et al.* (21) calls attention to the similarities of protein-carbohydrate interactions found in microbial adhesion systems to those employed by the host and notes that the latter interactions are involved in specificity but not tight binding of the receptor/ligand pairs. Tight binding appears to be promoted by protein-protein or protein-lipid interactions. This principle has been demonstrated for neutrophil recruitment where

recognition is mediated by protein (selectin)-carbohydrate (sialyl Le) binding but tight binding and flattening are the result of protein-protein (integrin/ligand) or protein-lipid binding. Similarly, St. Hilaire *et al.* have shown that the adhesion of the B-subunit (one of the smallest known lectins) of the VTEC holotoxin invokes both protein-carbohydrate (for targeting the toxin) and protein-lipid interactions (for entry of the toxin into the cell) which are also reminiscent of the mode of action of [butulinim] <u>botulism</u>, pertussis and diphtheria toxins (22). The generality of this motif requires structural and energetic studies on a large array of protein-carbohydrate-lipid-mediated biological recognition systems.

The table at page 16, line 14, was amended as follows:

<u>Table 1</u>

Adhesion Molecules Examined Under Shear

Adhesion [Molecule] <u>Molecules</u> Expressed on Optimal Function Conditions

	Leukocyte	Endothelium	Shear	Static
E-selectin	-	+	+	-
P-selectin	-	+	+	[-] <u>+/-</u>
L-selectin	+	-	+	-
MAdCAM-1	-	+	+	+
PNAd-1	+	+	[+/-] <u>±</u>	<u>-</u>
VCAM-1	+	+	[-/+] <u>±</u>	+
ICAM-1	+	+	[-] <u>+/-</u>	+
Mac-1	+	-	-	+

[1-LFA-1] LFA-1	+	-	-	[+] +/-
VLA4	+	-	[-/+] ±	+
beta-1	+	+	-/+	+
LPAM	+	-	+	+

The paragraph at page 18, line 1, was amended as follows:

Leukocytes that traffic in the blood are variously classed as a) lymphocytes, b) neutrophils, c) monocytes and d) platelets. Other cells that interact with or are derived from blood borne cells include antigen presenting cells (M cells, dendritic cells, macrophages) and cells that elaborate or secrete pharmacologically active compound (mast cells, eosinophils). The lymphocyte population includes subsets of antigen-reactive T cells defined by different functional roles they play (cytotoxic, helper cell, suppressor, etc.) and the combination of surface antigens or receptors they display. Two distinct subsets of T cells are instrumental in directing the immune response of the host into cell-mediated immune response (Th1) or predominantly a humoral immune response (Th2). Another lymphocyte population, the B cells, is characterized by the presence of membrane-bound immunoglobulins, initially monomers of IgM and later, IgD molecules and, after maturing into plasma cells, produce and secrete immunoglobulins.

The paragraph at page 18, line 20, was amended as follows:

Macrophages develop from blood-borne monocytes and bear a number of cell surface receptors for antibody, complement and various cell-cell interactions that promote movement through endothelia and epithelia. Dendritic cells are also large,

motile cells and, like macrophages, are involved in the processing/presentation of antigens to lymphocytes.

The paragraph at page 19, line 27, was amended as follows:

Epithelial cells line the luminal surfaces of the intestinal tract, genitor-urinary tract, upper respiratory tract and various organs of the mammal. Epithelial cells express many members of the integrin family and possess a host of different glycoconjugates that function as counter-receptors for pathogen adhesion molecules (PAMs).

Examples of nervous system cells include astrocytes, glial cells, schwann cells and neurons. The dominant host adhesion molecules found on nervous system cells are NCAM and ICAM. Ligand counter-receptors that bind to PAM are sialic acid-rich structures. [Examples of endothelial cells bearing ICAM-1, VCAM-1, MAdCAM-1 (Peyer's Patch) PNAd-1 (peripheral lymph node).]

The paragraph at page 20, line 4, was amended as follows:

Endothelial cells may display one or more adhesion [molecule] molecules depending on (a) stimulation by inflammatory mediators and (b) their location in tissue or an organ environment. The ICAM subfamily is generally expressed on endothelial cells as a consequence of stimulation by inflammatory mediators including [lipopolysasscharide] lipopolysaccharide, [τ-interferon] γ-interferon, interleukin-1 and tumor necrosis factor (TNF) elaborated during infections or tissue damage. VCAM has induction kinetics and function similar to ICAMs but interacts only with the VLA-4 integrin while ICAMs bind to LFA-1 integrin. Examples of dominant host adhesion

molecules on endothelial cells include ICAM-1, VCAM-1, MAdCAM-1 (Peyer's patch), and PNAd-1 (peripheral lymph node).

The paragraph at page 20, line 15, was amended as follows:

Lymphocytes in the blood enter lymph nodes by binding to specialized "high" endothelial cells. Molecules, termed "addressins" selectively expressed on specialized HEV in different types of lymph nodes function as homing receptor ligands. Thus, endothelial cells expressing MAdCAM-1 are found in the high endothelial venules of the Peyer's patches and lamina propra, and the lymphoid system associated with the intestine. Endothelial cells expressing PNAd-1 are found in peripheral lymph nodes.

The paragraph at page 22, line 6, was amended as follows:

Candidiasis – Research on *C. albicans* has shown that it expresses [an] a phosphomannoprotein on its surface responsible for the ability of hematogenous yeast cells to adhere ([presumabley] presumably to an integrin) on mouse splenic marginal zone macrophages and peripheral lymph nodes (29). *C. albicans* binding to [fibernectin] fibronectin in the extracellular matrix of blood vessels has been implicated as playing a direct role in promoting fungal adhesion for blood disseminated fungal disease (30).

The paragraph at page 23, line 23, was amended as follows:

A second property of PT is the ability to upregulate the function of the integrin family of leukocyte adhesion molecules. The ligation of a carbohydrate by the PT adhesion event upregulates the integrin CR3 (Mac-1) which allows the second [adhesion]

adhesin FHA, a specific ligand for CR3, to adhere and trigger uptake and survival of the bacteria in the macrophage. Thus, the PT adhesion has two functions in the infectious process: address recognition and signaling the macrophage to increase receptor sites for the organism.

The paragraph at page 25, line 27, was amended as follows:

Two forms of adherence derive from the expression of eaeA genes and/or plasmid encoded loci (40, 41, 42). The first or initial (localized) adherence is promoted by an 19 kDa EAF fimbrial [adhesion] adhesin referred to as the bundle forming pilus (BFP). The BFP [adhesion] adhesin causes adherence to the surface of the microvilli and the initiation of events that lead to effacing. Interestingly, the amino acid sequence of BFP of *E. coli* is similar to the pili of *Vibrio cholerae, Neisseria gonorrhoeae, Neisseria meningitides,* and *Pseudomonas aeuroginosa,* all of which are members of the type IV fimbrial family. It is proposed that the 19 kDa [adhesion] adhesin protein reacts with a carbohydrate ligand on the epithelial cell or, less likely, a specific carbohydrate epitope associated with mucin. This adherence and subsequent microcolonization event is followed by the transduction of a signal that results in elevated intracellular calcium levels, activation of host cell protein tyrosine kinases, fluid secretion and in severe verotoxic *E. coli* infections, profound changes in cytoskeletal structures. A second adherence event promoted by a chromosome-encoded 94-kDa outer membrane protein (OMP) containing an adhesion structure referred to as intimin permits the organism to adhere intimately to the epithelial cell plasma membrane and appears to amplify cell signaling leading to marked effects on cytoskeletal proteins of the epithelium and, in

some instances, to invasion of the submucosa. The amino acid sequence of *E. coli* intimin is highly similar to those of the invasions of *Yersinia pseudotuberculosis* and *Y. enterocolitica* (44). Invasins bind with a high affinity to members of the beta-1 family integrin receptors to mediate the efficient uptake of bacteria. There is reason to believe, therefore, that OMP adhesions are used by pathogenic *E. coli* to pass through beta 1 integrin doors (in contrast to beta 2 integrins in respiratory infections) and maneuver along the cytoskeleton of epithelial cells.

The paragraph at page 26, line 28, was amended as follows:

Helicobacter pylori has effectively colonized the majority of the world's population and is now accepted as the major cause of chronic gastritis and the formation of peptic ulceration (45). The bacterium is tropic for epithelial cells and the mucus layer in the stomach lining. Adherence to gastric epithelial cells is mediated by lectin-like [adhesions] <u>adhesins</u> interacting with fucosylated blood-group antigens associated with blood-group O phenotype (46). Surface epithelial degeneration is a probable result of the activity of bacterial products including cytotoxins, urease and pro-inflammatory products such as LPS.

The paragraph at page 29, line 24, was amended as follows:

<u>Herpesvirus.</u> Of all known viral proteins, few have significant sequence similarity to host cellular proteins but viral agents rely on recognition molecules on the host[,] cell for attachment and entry. However, the RNA retroviruses and two classes of DNA viruses[ ], the poxviruses and herpesviruses, employ molecular mimicry of

cytokines to subvert host cellular functions (20). The herpesvirus chemokine-receptor homologs mimic host membrane proteins [transmiting] <u>transmitting</u> a signal to the cytoplasm of host leukocytes that ensures a cytosolic milieu for herpesvirus replication and/or the establishment of latency.

The paragraph at page 30, line 1, was amended as follows:

The revolutionary conclusion the inventors have drawn from these studies is that most, if not all, pathogens have "learned" to infiltrate the host's network by using adhesion molecules that functionally mimic those of the host. The applications of the present [inventors] <u>inventors'</u> understanding of the functional and molecular character of prokaryotic adhesion molecules has led to the development of a new generation of diagnostic reagents, therapeutic compounds and vaccines.

The paragraph at page 30, line 10, was amended as follows:

The inventors <u>have</u> [develop] <u>developed</u> new reagents to detect potent immunogens for immunization against functionally similar but antigenically distinguishable adhesion molecules both of microbial origin and identified through "*in vitro* evolution". In addition new adjuvants are developed that recruit a specific population of immunologically competent [cell] <u>cells</u> into organ and tissue sites (i.e.[.], mucous membrane of the intestinal tract or nasopharyngeal region) where infectious adhesion events are likely to take place.

The paragraph at page 30, line 33, was amended as follows:

The function and characteristics of several pathogen-host cell adhesion systems have been identified by the inventors using an *in vitro* shear assay system. These host-parasite adhesion systems include but are not limited to verocytotoxic *E. coli, T. foetus, C. albicans*, and Hanta virus. Monoclonal antibodies have been developed against microbial adhesion factors to (1) aid in the detection and characterization of adhesions and their counter receptors on target cells and (2) define the dynamics of *in vitro* adherence events with appropriate target [cell] <u>cells</u>. The invention defines the nature and function of adhesion interactions in each *in vitro* target cell-pathogen system.

The paragraph at page 31, line 30, was amended as follows:

To prepare and use in vaccine formulations, the integrin-like attachment molecule (adhesin) [are] <u>is</u> defined and prepared as described herein. The key to success is dependent on (1) an amino acid sequence of the adhesive site of the [adhesion] <u>adhesin</u> that is encoded by microbial genes, hence is foreign (immunogenic) to the mammal and (2) presentation to the immune apparatus is in an aggregated form or a vehicle that stabilizes and protects it from degradation [in vivo] <u>*in vivo*</u>.

The paragraph at page 32, line 3, was amended as follows:

The integrins VLA, Leucam and cytoadhesions, in their native and functional form, are not used in a vaccine preparation because they are of host origin. Instead, microbial peptide homologs of the host-s integrin molecules that react with similar ligands on host cells or extracellular matrix proteins are used. Alternatively, or in conjunction thereto, molecules developed via "*in vitro* evolution"[ ], such as through

phage-display selection, may be used. In the thesis, the parasite or pathogen has acquired, by chance or, more likely, genetic piracy, a glycoprotein, glycolipid or carbohydrate structure that is functionally similar but antigenically distinct from the host receptor molecule (integrins, [selections] selectins or carbohydrate, protein or lipid ligand structures).

The paragraph at page 32, line 29, was amended as follows:

The demonstration of effective blocking of adhesion events involved in well defined infectious disease models has provided the basis for developing new vaccines, therapeutics, and diagnostics for many bacterial, viral, fungal, and protozoan infections. This "Adhesion Blocking Technology" (ABT) generates a serried of new products and applications for use in both humans and animals. A few examples of pathogens whose trafficking in the host is a function of adhesion-mediated events and for which effective new and novel diagnostics, therapeutics, and vaccines consisting of or containing adhesion-based reagents are developed include, for example, *Salmonella, Shigella, Vibrio, Yersinia*[;], *Bordetella*[;], *Legionellas*[;], *Candida*[;], *Helicobacter*[;], *Neisseria*[;], *Histoplasma*[;], *Leishmania* species[;], Influenza, Hantavirus, HIV virus[;], *Escherichia coli* (VTEC) [;], *Trichomonas, Eimeria, Trypanosoma*[;], [*Epstein-Barr virus*] Epstein-Barr virus[;], *Pneumococcus, Streptococcus*[;], *Rubella, Herpes*[;], *Staphylococcus*[;], *Chlamydia* and *Giardia.*

The paragraph at page 35, line 24, was amended as follows:

Antisera are generated against each of seven synthetic peptides corresponding to constant and variable sequences of the pili from gonococcal strain MS11 and were assayed for their ability to crossreact with intact pili from both homologous and heterologous strains as in "Antibodies to peptides corresponding to a conserved sequence of gonococcal pilins block bacterial adhesion." Rothbard, J.B., Fernandez, R., Wang, L., Teng, N.N., Schoolnik, G.K., Proc. Natl. Acad. Sci. USA, Feb. 1985, Vol. 82, No. 3, pp. 915-9. The peptides elicit roughly equal antipeptide responses but vary substantially in their ability to elicit antisera that crossreacted with intact pili. Of the antisera to peptides corresponding to [resions] regions of conserved sequence, antisera directed against residues 69-84 are the most efficient in binding pili from all strains tested in both solid-phase assays and immunoblots. Anti-69-84 also efficiently precipitate a tryptic fragment of pili known to bind human endocervical cells. Sera against the two peptides (121-134 and 135-151) previously shown to contain strain-specific epitopes crossreact with MS11 pili equally well, but differ in their ability to bind pili from heterologous strains. Anti-121-134 is strain-specific whereas anti-135-151 bind all pili tested. Each of the sera is examined for its ability to inhibit bacterial adhesion to a human endometrial carcinoma cell line. Sera generated against residues 41-50 and 69-84 successfully inhibit a heterologous gonococcal strain from binding.

The paragraph at page 37, line 27, was amended as follows:

Research into immunity to complex intracellular parasites has recently placed emphasis on the identification of peptide sequences recognized by T-cells, often with the dual objectives of finding species-specific protective epitopes, and of understanding

selection of Th1 versus Th2 response patterns, see "Adjuvants, endocrines and conserved epitopes; factors to consider when designing ["] therapeutic vaccines". Rook, G.A., Stanford, J.L., Medical Microbiology, UCL Medical School, London, U.K., Int. J. Immunopharmacol. (England), Feb. 1995, Vol. 17, No. 2, pp. 91-102.

The paragraph at page 39, line 3, was amended as follows:

Immunization protocol: Primary immunization antigens were adjusted to 10-20 μg of adhesion vaccines suspended in 0.5 mlPBS and emulsified in CytRx® [TiterMax™] <u>TiterMax®</u> #R-1 at a 50/50 ratio. In all cases, the subcutaneous (SC) route was used to avoid a toxic reaction in mice. Immunized mice were bled at day 14 to test antibody responses by ELISA. If a low titer was found, the mice were boosted with similar dose of antigen and bled and tested at day 28. This procedure was repeated at 2 week intervals until the desired antibody titers for both antigens were achieved.

The paragraph at page 39, line 14, was amended as follows:

ELISA screening protocol: ELISA assays employed Costar® universal covalent surface immuno assay plates and standard protocols for binding of the bacterial antigens. The system employed a two or three stage development system in which the [adhesion] <u>adhesin</u> or [verotxin] <u>verotoxin</u> was covalently bound to the 96 well assay plates by UV cross linking. The first stage anti-adhesion specific mouse serum of hybridoma supernatant antibodies were diluted and incubated in the plate wells after the adhesions were bound and the plates blocked with BSA. After washing to remove non-specifically bound first stage reagents, a peroxidase coupled anti-mouse second stage antibody was

added to the test wells, incubated, and washed. Substrate was then [be] added to the wells to develop the assay which was subsequently read by an automated ELISA plate reader. If the desired sensitivity was not achieved, a third stage to amplify signals was employed.

The paragraph at page 40, line 9, was amended as follows:

Preparation of target cells[.] – Freshly isolated human umbilical-cord endothelial cells (HUVEC) and commercially purchased HUVEC, which are Factor VII and LDL-receptor positive (cultured in endothelial-cell growth media (Clonetecs, EGM)), or E-selectin cDNA transfectants were grown to confluence on the internal surface of sterile glass 1.36 mm diameter capillary tubes (Drummond Scientific, Broomall, Penn) at least 24 hours prior to shear experiments. Four hours prior to the assay, the endothelial cells were treated with IL-1 (1 unit/ml) to induce E-selectin and other adhesion molecule expression.

The paragraph at page 43, line 30, was amended as follows:

Materials and Methods – Plain immunomagnetic beads were obtained commercially, e.g., from Dynal, and coated with adhesion of SLT mAbs using a protocol recommended by Dynal. In essence, the beads were mixed with an appropriate amount of mAb for 30 min. at 4°C, collected in a magnetic particle concentrator, washed 5 times and finally suspended in buffer. Various concentrations of VTEC suspended in phosphate-buffered saline (PBS) were reacted with the coated beads to determine the capture efficiency of the beads. Cells attached to the beads were stained with DAPI and

examined using epifluorescence microscopy to determine the number of attached cells. To detect slt in broth culture supernatant fluids, magnetic beads coated with [anti-salt] anti-slt were used to capture free slt and identified using a sandwiching technique involving a follow-on fluorescent labeled anti-slt.

The paragraph at page 44, line 10, was amended as follows:

Suspensions of *E. coli* strains, both 3A (from R.A. Wilson, Penn State University) and 932 (from U.S. E.P.A.), were grown on and harvested from blood agar plates and tryptone medium and used live or fixed in formalin for adherence to magnetized beads and for the conduct of the shear analyses. Upon incorporation of the capillary tube lined with bovine epithelial cells ([See] see above) in the loop system, a flow-induced shear force was established as a pulsatory wave flow peaking at 2 dynes, using Hanks balanced salt solution, HEPES (pH 7.0) as the medium. *E. coli* coated beads, suspended in PBS were infused into the shear flow via an injection port. Interactions of *E. coli* coated beads with epithelial cells were observed by video microscopy and recorded to video tape as a permanent record and for off-line computer image analysis. Adhesion of bead-bound *E. coli* was analyzed for types of adhesive interactions (rolling or sticking), characteristics (single beads or aggregates), and numbers of adhesive interactions over an interaction interval of ten minutes for the analysis of each condition. Hybridomas and monoclonal antibodies have been produced from spleen cells of immunized mice that recognize various cell surface determinants of the 0157 strain of *E. coli*. The demonstration of [Shear] shear dependent adhesion of 0157:H7 to bovine intestinal cells confirmed the presence and function of microbial attachment molecules and ligand structures on bovine

cells. Adherence was dependent on culture conditions (growth on blood agar) for the organism that appeared to promote the development of adhesions. Sera recognize antigenic differences promoted by cultural conditions in "broth grown or blood agar grown" 0157 *E. coli*. This data suggests that blood agar influences the development of specific cell surface adhesions recognized by these antibodies not found in cells grown in broth. Capture of *E. coli* 0157:H7 from suspension is dependent on the type and quantity of magnetic particle used, as well as the incubation procedures. Up to 98% of the cells in a $1x10^5$ CFU/ml can be captured under laboratory conditions using these methods. Only 60% of attached cells were removed from the magnetic particles by elution agents. Nearly 100 percent of 0157 inoculated into ground beef samples were detected by a refinement of the immunomagnetic separation (IMS) procedure.

The paragraph at page 46, line 29, was amended as follows:

Candida albicans is the most common cause of opportunistic fungal diseases in humans and has become the fourth leading cause of cases of nosocomial blood stream infections (15). An important step in the pathogenesis of disseminated candidiasis appears to relate to the ability of *Candida* cells to adhere to specific tissue locations within the host (7). The search for the appropriate fungal molecules is not trivial, however, as it has been shown that the surface antigenic makeup of *C. albicans* is variable both *in vitro* (3,4,5) and *in vivo* (6). Recently, Cutler *et al.* isolated the candidal [adhesions] <u>adhesins</u> responsible for adherence of *C. albicans* yeast cells to murine splenic marginal zone macrophages and macrophages in specific areas of peripheral lymph nodes (10). The [adhesions] <u>adhesins</u> are part of the mannan portion (12) of the

phosphomannoprotein complex (PMC) and [represents] represent a major part of the cell surface. One [adhesion] adhesin has been identified as a β-1,2-linked tetramannose located in the acid-labile part of the PMC and another [adhesion] adhesin resides in the acid-stable part of the complex (11). Detection of mannan adhesins in the serum of patients will thus prove to be a reliable indicator of disease. The adhesins are produced in abundance during growth of the fungus and are readily shed from the cell surface. Using high affinity monoclonal antibodies specific for candidal adhesion moieties, leads to the development of a rapid and reliable test for disseminated candidiasis under the invention.

The paragraph at page 47, line 28, was amended as follows:

The approach to a diagnostic solution resides with the early and rapid detection of candidal antigens in the body fluids or cells of patients with highly specific monoclonal antibodies (mAbs) directed against candidal antigens shed or released by the organism as it begins to grow and traffic in the body. The invention tests a panel of mAbs specific for an array of candidal cell surface antigens for the detection of candidal antigens in infected mice and humans. The development and use of anti-adhesion monoclonal antibodies and monoclonal antibodies directed to undefined cell surface determinants shed by or extracted from *Candida albicans in vitro* may be for the detection of candidal antigens in the body fluids and cells of infected mice and humans. The inventors [develop] developed a Candida peptide with an amino acid sequence which mimics a region of the phosphomannoprotein adhesion of [C. albicans] *C. albicans*.

The paragraph at page 48, line 10, was amended as follows:

The invention provides a key assay to detect the presence of *Candida* adhesions in serum and on host cells. The assay uses an antibody capture/sandwich ELISA method. Capture antibodies specific for *Candida albicans* antigens were used to coat the surface of polystyrene microtiter plates. After appropriate washing away of unbound capture antibody and blocking of unreacted sites on the plastic, test serum that contain *Candida* antigens was added to the antibody-coated wells, incubated and washed to remove unbound serum. A secondary antibody specific for the antigen was added to the wells, allowed to react with antigen bound to the capture antibodies and washed to remove all unbound materials. A tertiary antibody, which is specific for the secondary antibody and to which an appropriate enzyme is covalently coupled, was added to the wells to allow binding to all secondary antibody in the wells. After washing away unbound tertiary antibody, an appropriate chromogenic substrate specific for the enzyme on the tertiary antibody was added to the wells. As compared to appropriate positive and negative controls, a color reaction in the wells allows determination of the presence of *Candida* antigen [was] in the original test serum.

The paragraph at page 56, line 24, was amended as follows:

The isolation of a pathogen's adhesion (attachment) molecule (PAM) which mimics that expressed on host cells begins with its detection and characterization in the [inventors] <u>inventors'</u> *in vitro* shear assay system using target cells that express the ligand for the adhesion molecule or purified ligands coated on the luminal surface of a capillary tube reaction chamber. The technique for establishing various adhesive substrates on the

internal surface of small capillary tubes for the analyses under high and low physiological shear forces of any type of cell-cell adhesive interaction has been developed and perfected by the inventors (Bargatze, R., *et al.* 1994. J. Immunol. 152: 5814-5825 [.,] ; Jutila, M., *et al.* 1994. J. Immunol. 153: 3917-3928 [.] ; Bargatze, R., *et al.* 1994. J. Exp. Med. 180: 785-792 [.]).

The paragraph at page 57, line 5, was amended as follows:

The detection and characterization of PAMs and their ligands involves the use of an analytical *in vitro* shear flow apparatus (See Figure 2) that provides a reproducible real-time monitoring and quantification of microbial adhesive interactions with a panel of ligand assemblies displayed on immobilized substrates or cells of the endothelia or epithelia or other target cells during simulated physiological shear. The system consists of a closed capillary loop in which fluids are recirculated via a peristaltic pump. The infusion of cells injected into the loop brings about an encounter with monolayers of target cells coating the internal surface of the capillary tubes reminiscent of blood flow in the vascular system. The subsequent adhesive interactions of microbial cells and target cells or ligand bearing substrates are analyzed with the use of a professional-grade video data acquisition and recording system. The Macintosh® computer system (Apple [Computers] Computer®, Inc., Cupertino, CA), LG-3 video frame grabber board, (Scion Corporation, Frederick, MD), and Image software (NIH, Bethesda, MD) are customized for real-time and off-line video analysis of adhesion events.

The paragraph at page 63, line 3, was amended as follows:

All studies on the blocking of adhesion interactions with anti-adhesin mAbs and peptides are conducted on the [Montana ImmunoTech (MIT)] <u>LigoCyte® Pharmaceuticals, Inc.</u> Shear Analysis System described herein.

The paragraph at page 65, line 2, was amended as follows:

<u>Immunization protocol</u>: Balb/c mice, ranging in age from 8 to 12 weeks, are used for hybridoma and antibody production. Primary immunization antigens are adjusted to 10-20 μg of soluble adhesion molecule or glycoconjugates suspended in .5 ml PBS or $5x10^6$ or $5x10^7$ formalin-treated cells are emulsified in [CytRx^7] <u>CytRx®</u> [TiterMax^J] <u>TiterMax®</u> #R-1 at a 50/50 ratio. In all cases, the subcutaneous (SC) route is used to avoid a toxic reaction in mice. Immunized mice are bled at day 14 to test antibody responses by ELISA or agglutination of intact cells. If a low titer is found, the mice are boosted with similar dose of antigen and bled and tested at day 28. This procedure is repeated at 2 week intervals until the desired antibody titers for both antigens [were] <u>are</u> achieved.

The paragraph at page 65, line 18, was amended as follows:

<u>ELISA screening protocol</u>: ELISA assays employ [Costar] <u>Costar®</u> universal covalent surface immuno assay plates and standard protocols for binding of the bacterial and host antigens. The system employs a two or three stage development system in which the adhesion molecule [was] <u>is</u> covalently bound to the 96 well assay plates by UV cross linking. The first stage anti-adhesin specific mouse serum or hybridoma supernatant antibodies [is] <u>are</u> diluted and incubated in the plate wells after the adhesion

molecules are bound and the plates blocked with BSA. After washing to remove non-specifically bound first stage reagents, a peroxidase coupled anti-mouse second stage antibody is added to the test wells, incubated, and washed. Substrate is then added to the wells to develop the assay which is subsequently read by an automated ELISA plate reader. If the desired sensitivity is not achieved, a third stage to amplify signals is employed.

The paragraph at page 66, line 2, was amended as follows:

<u>Hybridoma fusion protocol</u> Anti-adhesion hybridomas are subcloned and selected as soon as hybridoma cell numbers permit. Subcloning is performed in 96-well plates by limiting dilution in [AHAT@] <u>HAT</u> medium. Upon successful ELISA screening of mAb-positive subclones, the hybridomas are adapted to serum-free medium for bulk production of anti-adhesin mAbs.

The paragraph at page 72, line 2, was amended as follows:

Many microbial attachment molecules, like the adhesion molecules (selectins) of inflammatory cell (leukocytes and endothelial cells) systems, are defined as lectin-like structures or carbohydrate binding proteins (CBP) that mediate adhesive interactions by recognition of carbohydrates on target cells (See: Microbial Lectins and Agglutinins. 1996. John Wiley and Sons, N.Y. and Jutila, M.A. *et al.* 1989. In: Leukocyte Adhesion, [Ediited] <u>Edited</u> by Springer, *et al.* Springer-Verlag, p. 211-219). These attachment molecules are chemically defined as glycoproteins and control a myriad of biological events. Microbial CBP receptors, like selectins on inflammatory cells, serve as

molecules of recognition in cell-cell interactions. BDP receptors bind reversibly and noncovalently with mono or oligosaccharides, both simple and complex whether free in solution or on [cells] <u>cell</u> surfaces.

The paragraph at page 74, line 2, was amended as follows:

Pathogenic organisms have acquired an array of protein molecules that functionally mimic those involved in regulating the cytoskeleton of eukaryotic cells. These so-called virulence proteins [interfere] <u>interfere</u>, for example, with a signaling cascade containing small guanosine triphosphate (GTP)-binding proteins (-Rho, Ras, Rac, Cdc42, etc.) that direct the function of the actin network of host cells. The virulence proteins appear to bind in a very specific manner to GTP-binding proteins and [promotes] <u>promote</u> rearrangements of the actin network that benefit the microbe.

<u>IN THE CLAIMS</u>

58. (Amended) The vaccine of claim 55, wherein said pathogen adhesin molecule <u>functionally</u> mimics [an] <u>a ligand for said host</u> adhesion molecule [of the host].

62. (Amended) The vaccine of claim 59, wherein said <u>host adhesion molecule is a receptor for an integrin, and said host adhesion molecule is a</u> member of the immunoglobulin superfamily [is] selected from the group consisting of ICAM-1, ICAM-2 or ICAM-3, VCAM, NCAM and PECAM.

64. (Amended) The vaccine of claim [55] 59, wherein said host adhesion molecule is a receptor for a selectin, and said host adhesion molecule presents a residue [pathogen adhesin molecule binds to a carbohydrate ligand] selected from the group consisting of residues of N-acetylneuraminic acid, sialic acid, N-acetylglucosamine, N-acetylgalactosamine, glucosamine, galactosamine, galactose, mannose, fucose and lactose.

105. (Amended) The therapeutic composition of claim 100, wherein said pathogen adhesin molecule functionally mimics [an] a ligand for said host adhesion molecule [of the host].

109. (Amended) The therapeutic composition of claim 106, wherein said host cell adhesion molecule is a member of the immunoglobulin superfamily [is] selected from the group consisting of ICAM-1, ICAM-2 or ICAM-3, VCAM, NCAM and PECAM.

Current Claims under examination pursuant to restriction, as set forth in OA dated April 10, 2002 - elected material in bold - WITH AMENDMENTS

55. A vaccine comprising a pharmaceutically acceptable carrier and an isolated pathogen adhesin molecule or immunogenic fragment thereof, wherein the pathogen adhesin molecule or immunogenic fragment thereof specifically binds to an adhesion molecule on a host cell or extracellular matrix under shear conditions *in vitro,* and wherein said vaccine induces a therapeutically effective immune response against the pathogen.

56. The vaccine of claim 55, wherein said shear conditions are selected from the group consisting of physiological shear conditions as characteristically found in the: (1) vascular system; (2) respiratory system; (3) gastrointestinal tract; and (4) urinary tract.

57. The vaccine of claim 55, wherein said host cell is selected from the group consisting of leukocytes, **endothelial cells**, epithelial cells and cells of the nervous system.

58. The vaccine of claim 55, wherein said pathogen adhesin molecule <u>functionally</u> mimics [an] <u>a ligand for said host</u> adhesion molecule [of the host].

59. The vaccine of claim 55, wherein said host adhesion molecule is a receptor for a host ligand selected from the group consisting of C-type lectins, **selectins, integrins**, members of the immunoglobulin superfamily and cytokines.

60. withdrawn

61. withdrawn

62. The vaccine of claim 59, wherein said host adhesion molecule is a receptor for an integrin, and said host adhesion molecule is a member of the immunoglobulin superfamily [is] selected from the group consisting of **ICAM-1**, ICAM-2 or ICAM-3, VCAM, NCAM and PECAM.

63. The vaccine of claim 55, wherein said host adhesion molecule is selected from the group consisting of **proteins, glycoproteins**, glycolipids and carbohydrates.

64. The vaccine of claim [55] 59, wherein said host adhesion molecule is a receptor for a selectin, and said host adhesion molecule presents a residue [pathogen adhesin molecule binds to a carbohydrate ligand] selected from the group consisting of residues of N-acetylneuraminic acid, sialic acid, N-acetylglucosamine, N-acetylgalactosamine, glucosamine, galactosamine, galactose, **mannose**, fucose and lactose.

65. withdrawn

66. withdrawn

67. The vaccine of claim 55 wherein said host cell is selected from the group consisting of cytokine-stimulated endothelial cells and endothelial cells expressing **ICAM-1**, CAM-1, MAdCAM-1 and PNAd-1.

68. The vaccine of claim 55, wherein said pathogen is selected from the group consisting of viruses, bacteria, protozoa and **fungi**.

69. withdrawn

70. withdrawn

71. withdrawn

72. The vaccine of claim 68, wherein said pathogen is a fungus.

73. withdrawn

74. withdrawn

75. withdrawn

76. The vaccine of claim 68, wherein said pathogen is selected from the fungal parasite group consisting of *Blastomyces, Aspergillus, Cryptococcus,* ***Candida,*** *Histoplasma, Coccidioides* and *Phycomycetes.*

77. withdrawn

78. withdrawn

79. withdrawn

80. The vaccine of claim 55, wherein said host cell is selected from the group of respiratory system cells consisting of alveolar macrophages and **endothelial** and epithelial cells of the nasopharynx and alveoli.

81. withdrawn

82. withdrawn

83. The vaccine of claim 55, wherein said vaccine further comprises peptide domains of glycoprotein adhesion molecules on the cell surface of microbes selected from a group consisting of *Escherichia coli*, *Yersinia pseudotuberculosis, Helicobacter pylori, Vibrio cholera, Salmonella typhi, Salmonella typhimurium, Shigella dysenteriae, Leishmania, Giardia lambia, Entamoeba histolytica,* ***Candida albicans*** and *Harnia alvae*.

84. withdrawn

85. withdrawn

86. The vaccine of claim 55, further comprising a delivery system displaying said pathogen adhesion molecule or immunogenic fragment thereof.

87. The vaccine of claim 86, where said delivery system is selected from the group consisting of phage, a live vector, liposomes, M13 phage, cowpea mosaic virus, alginate gels, peptide conjugates, and glycoconjugates.

88. withdrawn

89. A vaccine comprising a pharmaceutically acceptable carrier and an isolated pathogen adhesin molecule or immunogenic fragment thereof, wherein the pathogen adhesin molecule specifically binds to an adhesion molecule on a host cell or extracellular matrix under physiologic shear conditions *in vitro,* and wherein said vaccine induces a therapeutically effective immune response against the pathogen.

90. A vaccine comprising a pharmaceutically acceptable carrier and an isolated pathogen adhesin molecule mimetic, wherein said mimetic induces a therapeutically effective immune response against the pathogen.

91. withdrawn

92. withdrawn

93. withdrawn

94. withdrawn

95. withdrawn

96. withdrawn

97. withdrawn

98. A diagnostic assay kit, comprising a peptide or oligopeptide that mimics the adhesive domain of a pathogen adhesin molecule, wherein said molecule specifically binds to an adhesion molecule on a host cell or extracellular matrix under shear conditions *in vitro*.

99. A diagnostic assay test composition comprising a glycolipid matrix displaying host adhesion molecules that bind to a carbohydrate selected from the group consisting of residues of N-acetylneuraminic acid, sialic acid, N-acetylglucosamine, N-acetylgalactosamine, glucosamine, galactosamine, galactose, **mannose**, fucose and lactose; wherein said host adhesion molecule binds specifically to a pathogen adhesin molecule under shear conditions *in vitro*.

100. A therapeutic composition comprising a pharmaceutically acceptable carrier and an isolated pathogen adhesin molecule or fragment thereof, wherein said pathogen adhesin molecule or fragment specifically binds to an adhesion molecule on a host cell or extracellular matrix under shear conditions *in vitro*.

101. The therapeutic composition of claim 100, wherein said composition inhibits one or more of the following events associated with infection by the pathogen of an infected host, said events being selected from the group consisting of: (1) recognition by the pathogen of specific host cells or extracellular matrix; (2) shear dependent attachment of the pathogen to host cells or extracellular matrix; (3) activation dependent adhesion of the pathogen; (4) signal transduction mediated by the pathogen; (5) transendothelial migration of the pathogen; (6) passage by the pathogen through epithelia; (7) colonization by the pathogen; and (8) binding of a toxin produced by the pathogen to host cells or extracellular matrix.

102. The therapeutic composition of claim 100, wherein said composition binds to members of the selectin family of host adhesion molecules.

103. The therapeutic composition of claim 100, wherein said composition binds to members of the immunoglobulin superfamily of host adhesion molecules.

104. The therapeutic composition of claim 100, wherein said composition binds to members of the integrin family of host adhesion molecules.

105. The therapeutic composition of claim 100, wherein said pathogen adhesin molecule functionally mimics [an] a ligand for said host adhesion molecule [of the host].

106. The therapeutic composition of claim 105, wherein the host adhesion molecule is a receptor for a host ligand selected from the group consisting of **selectins,**

integrins, members of the immunoglobulin superfamily, cytokines and guanosine triphosphate-binding proteins.

107. withdrawn

108. withdrawn

109. The therapeutic composition of claim 106, wherein said host cell adhesion molecule is a member of the immunoglobulin superfamily [is] selected from the group consisting of **ICAM-1**, ICAM-2 or ICAM-3, VCAM, NCAM and PECAM.

110. withdrawn

111. withdrawn

112. The vaccine of claim 55 formulated for mucosal delivery, wherein the vaccine is administered orally or intranasally.

113. (New) The vaccine of claim 55, wherein said pathogen adhesin molecule binds to a host adhesion molecule that binds to a selectin.

114. (New) The vaccine of claim 55, wherein said pathogen adhesin molecule binds to a host adhesion molecule that binds to an integrin.

3. **EXTENSION OF TIME**

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

[ ] Applicant believes that no extension of time is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

[X] Applicant petitions for an extension of time, the fees for which are set out in 37 CFR 1.17(a)-(d), for the total number of months checked below:

Total months requested	Fee for extension	[fee for Small Entity]
[X] one month	$ 110.00	**$ 55.00**
[ ] two months	$ 390.00	$195.00
[ ] three months	$ 890.00	$445.00
[ ] four months	$1,390.00	$695.00
[ ] five months	$1,890.00	$945.00

Extension of time fee due with this request: **$55.00**

If an additional extension of time is required, please consider this a Petition therefor.

[ ] An extension for __ months has already been secured and the fee paid therefor of $____ is deducted from the total fee due for the total months of extension now requested.

3. Fee Calculation

CLAIMS AS AMENDED						
	Claims Remaining After Amendment		Highest No. Previously Paid	Present Extra	at Rate of	Total Fees
Total Claims	60	**minus**	58	2	2 x $18 each=	+ $36
Independent Claims	8	**minus**	14	0	0 x $80 each=	+ $0
[ ] First presentation of Multiple dependent claim(s)				0	$260.00	+ $0
SUB-TOTAL =						**$ 36**
Reduction by ½ for filing by a small entity						**- $ 18**
TOTAL FEE =						**$ 18**

4. Fee Payment

[X] The Commissioner is hereby authorized to charge $ 253.00, which covers:

$180.00 for Information Disclosure Statement under 37 CFR 1.97(c)
$55.00 for one month extension of time
$18.00 for additional claims

[X] The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 CFR §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully submitted,

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